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*Original Article*

# Myocardial protection of dexmedetomidine in patients undergoing cardiac valve replacement under cardiopulmonary bypass

Xingang Qin[1*], Fan Li[1*], Chanjuan Yu[2]

*[1]Department of Anesthesiology, Fifth Affiliated Hospital, Xinjiang Medical University, Urumqi City, Xinjiang Uygur Autonomous Region, P. R. China; [2]Department of Anesthesiology, Third Affiliated Hospital (Tumor Hospital), Xinjiang Medical University, Urumqi City 830000, Xinjiang Uygur Autonomous Region, P. R. China. [*]Equal contributors and co-first authors.*

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**Abstract:** Objective: To clarify myocardial protection of metodetomidine during anesthesia induction for cardiac valve replacement (CVR) under cardiopulmonary bypass (CPB). Methods: From January 2016 to January 2017, a total of 76 patients undergoing CVR under CPB in our hospital were recruited in this study and randomly assigned to receive dexmedetomidine for anesthesia before CVR (observation group, n=41) or equivalent amounts of normal saline (control group, n=35). The two groups of patients were compared in the myocardial injury markers, and operative parameters at different time points (before anesthesia induction (T1), 30 min after aortic unclamping (T2), immediately after operation (T3), 6 h after operation (T4) and 24 h after operation (T5)), and the hemodynamic parameters and oxidative stress parameters at diverse time intervals (T1, after intubation (T6), immediately after sternotomy (T7), before CPB (T8), and 10 min after CPB (T9)). Results: The serum creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and cardiac troponin I (cTnI) levels were increased more remarkably at T2, T3, T4, and T5 than at T1 in both groups (P<0.05); the serum cTnI level at T3 (P=0.034), the serum CK (P=0.041, P=0.045), CK-MB (P=0.047, P=0.039), and cTnI (P=0.031, P=0.038) levels at T4, and T5 in the observation group were considerably lower than those in the control group. The heart rates (HR) at T6, T7, and T9 in the control group and the HR at T9 in the observation group were increased more remarkably than those at T1 in the same group (all P<0.001). The mean arterial pressure (MAP) values in the observation group rose more strikingly than those in the control group (all P<0.001). In the observation group, the serum superoxide dismutase (SOD) levels at T2, T3, T4, and T5 rose more remarkably than that at T1 (all P<0.001). In both groups, the serum malondialdehyde (MDA) levels rose more substantially at T2, T3, T4, and T5 than those at T1 (all P<0.001); the serum MDA levels at T2, T3, T4, and T5 in the observation group were remarkably lower than those in the control group (all P<0.001). Conclusion: Dexmedetomidine helps relieve oxidative stress and maintain hemodynamic stability during CPB; hence it has certain effect of myocardial protection.

**Keywords:** Cardiac valve replacement, cardiopulmonary bypass, anesthesia, dexmedetomidine, myocardial protection

## Introduction

Prior to cardiac valve replacement (CVR) under cardiopulmonary bypass (CPB), most patients already have cardiac injuries and are allergic to anesthetics. Particularly during the induction of anesthesia, the intensive hemodynamic fluctuations, plus surgical stimulation, aggravate myocardial injuries [1, 2]. Myocardial ischemia/reperfusion injury is an inevitable cause of myocardial injuries during CVR under CPB. Even worse, intense stress response, inflammatory response, physiological disorders and pathological changes triggered by surgical procedures further damage the myocardia. In this case, it is necessary to apply anesthetic preconditioning induced by myocardium-protecting drugs during CVR under CPB to guarantee the success of the surgery.

Dexmedetomidine, a highly selective a 2-adrenergic receptor agonist, produces multiple eff-

ects including sympathetic block, sedation and analgesia. It effectively suppresses the stress response induced by surgical traumas, and stabilizes hemodynamics [3]. Myocardial protection rendered by dexmedetomidine has captured much attention from many scholars. Moreover, animal experiments both in vivo and in vitro also indicate that dexmedetomidine is associated with significant improvements in the symptoms of myocardial ischemia and hypoxia, and myocardial ischemia/reperfusion injuries in rats [4-6]. Nevertheless, currently, dexmedetomidine is primarily used in providing myocardial protection for patients with cardiovascular disease undergoing non-cardiac surgery as well as in animal experiments. Whether dexmedetomidine can protect the myocardium during CVR under CPB remains controversial.

Therefore, this study presented here was designed to analyze myocardial protection of dexmedetomidine-based anesthesia for CVR under CPB, so as to clarify the myocardial protection rendered by dexmedetomidine and improve myocardial protection in patients undergoing CVR under CPB.

## Methods and materials

### *Patients*

The patients undergoing CVR under CPB in our hospital from January 2016 to January 2017 were enrolled in this study. Patients aged between 18 and 60 years old were eligible for enrollment if they showed surgical indications to CVR; the American Society of Anesthesiologists (ASA) of Class II or III; the New York Heart Association (NYHA) of Class II or III; no overt major organ dysfunction syndrome (MODS) involving in the liver, the kidney or the lung; the left ventricular ejection fraction (LVEF) ≥40%; no occurrence of cardiovascular events within the previous 30 days; no previous history of cardiac surgery; complete clinical records. This study got approval from the ethics committee in the hospital, and written informed consent was acquired from the patients (or their families). Patients younger than 18 years old or older than 60 years old were excluded if they had the LVEF<40%; occurrence of cardiovascular events within the previous 30 days, concomitant atrioventricular block, carotid atherosclerosis and MODS, or a previous history of cerebra stroke or cardiac surgery.

### *Anesthesia and intervention*

General anesthesia was induced among all the patients in the two groups. On arrival at the operating room, the patients were given oxygen by mask. The right upper extremity venous access was established and unclamped for blood gas analysis and monitoring of vital signs. Intravenous midazolam, sufentanil and etomidate, and rocuronium at respective doses of 0.05 mg/kg, 1 μg/kg, 0.3 mg/kg, and 0.6 mg/kg were injected for anesthesia induction, followed by tracheal intubation or mechanical ventilation. After successful anesthesia induction, the right internal jugular vein was punctured for intubation. Blood was infused through the main pathway whereas drugs were infused through the pathways on both sides. Subsequently, the central venous pressure was measured. For each patient in the observation group, prior to anesthesia induction, intravenous dexmedetomidine was injected at a dose of 0.5 μg/kg for 15 min, followed by intravenous infusion at 0.2 μg/kg/h until the completion of operation. By contrast, for each patient in the control group, an equal amount of normal saline was injected intravenously before induction of anesthesia, and maintained at the same rate till the end of operation. In both groups of patients, anesthesia was maintained with sevoflurane and sufentanil, including inhalation of 1-2% of sevoflurane, continuous intravenous drip of sufentanil at 0.4-0.7 μg/kg/h, and intermittent injection of cisatracurium at 0.15 mg/kg.

### *Outcome measures*

The myocardial injury markers, operative, hemodynamic and oxidative stress parameters at diverse time points were compared between the two groups. The primary outcomes were myocardial injury markers, while the secondary outcomes included operative, hemodynamic and oxidative stress parameters. Details are shown in the following sections.

### *Myocardial injury markers*

At different time points including before induction of anesthesia (T1), 30 min after aortic unclamping (T2), immediately after operation (T3), 6 h after operation (T4), and 24 h after operation (T5), 4 mL of fasting venous blood was extracted from each patient and centri-

**Table 1.** Demographic characteristics of the two groups

| Variable | Case | Male | Age | BMI | ASA | | NYHA | |
|---|---|---|---|---|---|---|---|---|
| | | | | | II | III | II | III |
| CG | 35 | 18 (51.43) | 51.9±4.84 | 26.4±1.24 | 21 (60.00) | 14 (40.00) | 19 (54.29) | 16 (45.71) |
| OG | 41 | 22 (53.66) | 52.3±4.51 | 25.9±1.31 | 25 (60.98) | 16 (39.02) | 24 (58.54) | 17 (41.46) |
| Statistic | | 0.124 | 0.106 | 0.134 | 0.157 | 0.162 | 0.204 | 0.196 |
| *P* value | | 0.0872 | 0.894 | 0.862 | 0.842 | 0.839 | 0.799 | 0.807 |

Note: CG denotes control group, and OG observation group.

**Table 2.** Operative parameters of the patients

| Variable | Case | CPB (min) | ACC (min) | IB (mL) | SD (mg) | TTE (h) |
|---|---|---|---|---|---|---|
| CG | 35 | 125.47±24.82 | 74.69±15.04 | 214.52±44.62 | 264.35±45.72 | 4.75±0.52 |
| OG | 41 | 126.047±25.68 | 75.13±14.85 | 216.28±46.07 | 266.04±46.17 | 4.81±0.49 |
| t | | 0.262 | 0.304 | 0.226 | 0.286 | 0.314 |
| P | | 0.742 | 0.703 | 0.772 | 0.716 | 0.689 |

Note: CG denotes control group, and OG observation group, CPB cardiopulmonary bypass, ACC aorta cross-clamping, IB intraoperative bleeding, SD sufentanil dosage, and TTE time to tracheal extubation.

fuged, from which serum was isolated. The enzyme-linked immunosorbent assay (ELISA) was performed for detection of the serum creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and cardiac troponin I (cTnI) of the patients with the use of a Beckman UniCal DxC 800 automatic biochemical analyzer. The kits for measurement of CK, CK-MB, and cTnI were all purchased from Beckman Coulter, USA.

*Operative parameters*

The operative parameters consisted of the duration of CPB, the duration of aorta cross-clamping, intraoperative bleeding, sufentanil dosage, as well as the time to postoperative tracheal extubation. The abovementioned operative parameters were compared between the two groups.

*Hemodynamic parameters*

The heart rates (HR) and the mean arterial pressure (MAP) of all the patients were documented at T1, after intubation (T6), immediately after sternotomy (T7), before CPB (T8), and 10 min after CPB (T9), respectively.

*Oxidative stress parameters*

Fasting venous blood (4 mL) was extracted from each patient at T1, T2, T3, T4, and T5, and then centrifuged, serum isolated. Serum superoxide dismutase (SOD) and malondialdehyde (MDA) of all the patients were detected using a Beckman UniCal DxC 800 automatic biochemical analyzer by the ELISA. The kits for SOD and MDA measurement were also purchased from Beckman Coulter, USA.

*Statistical analysis*

All the data were analyzed with the application of the SPSS software, version 19.0. Measurement data were described as mean ± standard deviation. The comparisons of the data at different time points were made by means of the repeated measures analysis of variance (ANOVA). Count data were detected using the chi-square test. $P<0.05$ was deemed to be statistically significant.

## Results

*Demographic characteristics*

A total of 76 eligible patients were randomly assigned to receive dexmedetomidine (observation group) or equal amount of normal saline (control group) in terms of a random number table. Gender, age, BMI, the ASA classification and the NYHA class of patients were well-balanced between the control group and the observation group (all $P>0.05$, **Table 1**).

*Myocardial injury markers at different time points*

The repeated measures ANOVA demonstrated that statistical differences were noted between

**Table 3.** Myocardial injury markers at different time points

| MIM | Group | T1 | T2 | T3 | T4 | T5 |
|---|---|---|---|---|---|---|
| CK (U/mL) | CG | 62.47±7.36 | 411.25±44.58 | 533.42±65.69 | 713.54±71.58* | 614.58±73.58* |
| | OG | 63.25±7.45 | 393.84±64.95 | 487.25±65.58 | 557.14±72.35 | 486.59±57.84 |
| CK-MB (U/mL) | CG | 13.04±2.35 | 24.08±3.53 | 46.41±5.51 | 63.37±7.38# | 45.52±5.91# |
| | OG | 13.45±2.41 | 22.04±3.19 | 40.14±5.02 | 50.04±6.45 | 35.95±4.25 |
| cTnI (ng/mL) | CG | 0.32±0.017 | 0.82±0.26 | 1.21±0.15Δ | 2.53±0.49Δ | 1.78±0.22Δ |
| | OG | 0.35±0.015 | 0.74±0.24 | 0.86±0.12 | 1.37±0.31 | 1.15±0.26 |

Note: MIM denotes myocardial injury marker, CG control group, and OG observation group. Comparison of CK at T4 and T5 between the two groups, *P<0.05 (t=4.524, 4.263; P=0.041, 0.045); comparison of CK-MB at T4 and T5 between the two groups, #P<0.05 (t=4.152, 4.752; P=0.047, 0.039); comparison of cTnI at T3, T4 and T5 between the two groups, ΔP<0.05 (t=5.262, 5.517, 5.094; P=0.034, 0.031, 0.038).

**Table 4.** Hemodynamic changes at different time points in the two groups

| HM | Group | T1 | T6 | T7 | T8 | T9 |
|---|---|---|---|---|---|---|
| HR (beat/min) | CG | 68.9±11.4 | 76.7±10.2* | 81.4±11.8* | 68.9±12.4 | 84.2±12.9* |
| | OG | 69.1±10.8 | 67.2±11.3 | 68.6±12.6 | 64.3±10.8 | 83.6±11.5* |
| MAP (mmHg) | CG | 72.4±10.3 | 65.2±8.24* | 61.3±8.1* | 56.8±11.0* | 63.2±11.3* |
| | OG | 73.1±11.2 | 75.3±10.2#,Δ | 73.6±10.3#,Δ | 69.7±8.14#,Δ | 74.2±10.8#,Δ |

Note: Compared within the same group at T1, *P<0.001, #P>0.05; compared between the two groups at the same time point, ΔP<0.001. HM denotes hemodynamic parameter, CG control group, and OG observation group.

the two groups in CK, CK-MB and cTnI at different time points; however, higher serum CK and CK-MB levels at T4 and T5, and higher cTnI levels at T3, T4 and T5 were observed in the control group. The serum levels of CK, CK-MB and cTnI were all higher at T2, T3, T4, and T5 than at T1 in both groups (**Table 3**).

*Operative parameters*

The duration of CPB, the duration of aorta cross-clamping, intraoperative bleeding, sufentanil dosage, as well as the time to postoperative tracheal extubation were generally similar between the two groups (P>0.05, **Table 2**).

*Hemodynamic changes*

According to the repeated-measures ANOVA, HR and MAP at different time points varied between the two groups. The MAP values at T6, T7, T8, and T9 were lower in the control group than in the observation group. The HR at T6, T7, and T9 were higher than that at T1 in the control group, whereas the HR at T9 was higher than that at T1 in the observation group. The MAP values at T6, T7, T8, and T9 were lower than that at T1 in the control group; conversely, the MAP values at T6, T7, T8, and T9 differed insignificantly from that at T1 in the observation group (P>0.05, **Table 4**).

*Oxidative stress parameters at different time points*

On the repeated-measures ANOVA, the MDA and SOD levels at different time points were different between the two groups. The serum MDA levels at T2, T3, T4, and T5 in the control group were higher, but the serum SOD levels at the same time points were lower than in the observation group. In both groups, the serum MDA levels at T2, T3, T4, and T5 were higher than those at T1; nevertheless, the serum SOD levels at T2, T3, T4, and T5 were largely similar to that at T1 in the control group (P<0.574; **Table 5**).

## Discussion

Myocardial protection during anesthesia in patients undergoing CVR under CPB has been a focus of current studies. Since dexmedetomidine is a highly selective a 2-adrenergi receptor agonist, it can specifically produce multiple effects such as sedation, analgesia, as well as relief of stress and inflammatory response. As a result, it is considered as an ideal preconditioning agent to alleviate the perioperative visceral injury [7-9]. The patients undergoing CVR under CPB tend to be complicated with various degrees of physiological disorders and pathological changes in anesthesia. In our current

**Table 5.** Oxidative stress parameters at different time points in the two groups

| OSP | Group | T1 | T2 | T3 | T4 | T5 |
|---|---|---|---|---|---|---|
| MDA (mg/L) | CG | 4.58±0.72 | 13.27±1.37* | 11.35±1.28* | 9.78± 0.85* | 7.58±1.34* |
| | OG | 4.61±0.86 | 11.05±1.25*,# | 8.06±1.22*,# | 6.53±0.54*,# | 5.12±0.68*,# |
| SOD | CG | 0.33±0.15 | 0.32±0.07 | 0.28±0.14 | 0.30±0.12 | 0.29±0.18 |
| | OG | 0.31±0.16 | 0.51±0.17# | 0.41±0.23# | 0.59±0.33# | 0.41±0.15# |

Note: Compared within the same group at T1, *P<0.001; compared between the two groups at the same time point, #P<0.001. OSP denotes oxidative stress parameter, CG control group, and OG observation group.

study, the patients in the control group showed a trend of rising HR but declining MAP during induction and maintenance of anesthesia; The HRs was significantly increased at T6, T7, and T9 versus T1, but the MAP values were dramatically decreased at T6, T7, T8, and T9 versus T1. However, after anesthesia induction, the patients in the observation group received intravenous injection of dexmedetomidine, and maintained the intravenous infusion till the end of operation, leading to effective alleviation of hemodynamic changes in the patients; the HR at T6, T7, and T8 differed mildly from that at T1, though the HR at T9 increased more significantly than that at T1; likewise, the MAP values at T6, T7, T8, and T9 were largely similarly to that at T1. Nevertheless, the HR and MAP values at the same time points of anesthesia differed greatly between the two groups. All this suggests that dexmedetomidine reduced excitability of the sympathetic nerves and stimulated vascular smooth muscle cells a 2, resulting in transient vasoconstriction, higher blood pressure, and a slower HR. It facilitates offsetting the trend of increasing HR but declining MAP in the patients undergoing CVR under CPB.

CK, CK-MB and cTnI are all measures for detecting the severity of myocardial injury, and they have high sensitivity and specificity. In our current study, it is of clinical significance that CK, CK-MB and cTnI were employed for evaluation of myocardial protection rendered by dexmedetomidine [10, 11]. As reported in a study, the inevitable myocardial ischemia/reperfusion injury during CPB results in release of a sea of CK, CK-MB and cTnI into the blood circulation [12, 13]. In a retrospective study, Cai et al. found that stress reaction, inflammatory response and physiological disorders were independent risk factors for cardiac injury in patients undergoing CVR under CPB, as significantly elevated serum levels of CK, CK-MB and cTnI were observed in the patients [14]. In our current study, the serum CK, CK-MB, and cTnI levels were higher at T2, T3, T4, and T5 than at T1 in both groups, suggesting that the implementation of CVR under CPB was inevitably associated with the consequences of myocardial injury and decreased cardiac function. Thus, it is necessary to conduct preconditioning for myocardial protection. Dexmedetomidine has biphasic effects on the cardiovascular system, with the initial role to promote vasoconstriction and the final role to reduce the excitability of the sympathetic nerve system and enhance vasodilation; the two effects effectively offset the trend of hemodynamic changes of the patients during the surgery, leading to fewer cardiovascular adverse events [15]. A study involving a rat model of myocardial ischemia reperfusion injury revealed that intraperitoneal injection of dexmedetomidine (at 5 μg/kg) for preconditioning inhibited the noradrenergic nerve activities, improved myocardial oxygen balance and rendered myocardial protection [16]. Animal studies demonstrate that specific binding of dexmedetomidine to cardiac α receptor in rats with myocardial ischemia/reperfusion injury is associated with reduced myocardial oxygen consumption, and improved cardia function [17]. Moreover, dexmedetomidine alleviates the stress and inflammatory response of the patients, and it also plays a role in reducing stress response and inflammatory cytokines as well as myocardial injury [18, 19]. In our current study, the serum CK and CK-MB levels at T4 and T5 were lower in the observation group than in the control group, and the serum cTnI levels at T3, T4, and T5 were lower in the observation group than in the control group, which indicates that dexmedetomidine has a remarkable myocardial protective effect.

Oxidative stress is a decisive step to mediate myocardial injury in patients undergoing CVR

under CPB because the release of numerous oxygen free radicals which are generated in the surgical procedures and by CPB-induced traumas further result in myocardial oxidative damage [20]. MDA is generally considered as a product of cell oxidation and reflects the release level of oxygen free radicals. SOD, one of the most important antioxidant factors, is effective in clearance of oxygen free radicals. Nevertheless, in our current study, though the serum MDA levels increased more significantly at T2, T3, T4, and T5 than at T1 in the two groups ($P<0.05$), the serum MDA levels at T2, T3, T4, and T5 in the observation group were remarkably lower than those in the control group ($P<0.05$); the serum SOD levels at T2, T3, T4, and T5 differed slightly from that at T1 in the control group ($P>0.05$), but significantly elevated serum SOD levels at T2, T3, T4, and T5 versus at T1 were noted in the observation group ($P<0.05$). All this implies that the use of dexmedetomidine facilities clearance of oxygen free radicals in patients undergoing CVR under CPB, improves the serum SOD levels, effectively alleviates the intensive stress and renders myocardial protection, though the mechanisms of action remains unclear. The serum MDA and SOD levels at T2, T3, T4, and T5 in the observation group were superior to those in the control group in our present study. It might be related to the following aspects; firstly, dexmedetomidine effectively attenuates the intensity of stress response due to its concomitant sedative, analgesic and hypnotic effects; secondary, it inhibits the release of adrealine, and increases cyclic adenosine monophosphate (AMP) in the coronary artery, hence directly rendering myocardial protection; finally, it also has an antisympathetic nerve effect and improves myocardial metabolism [21, 22]. In this regard, the abovementioned three mechanisms interact with each other to render synergistic myocardial protection.

In conclusion, dexmedetomidine attenuated oxidative stress and maintained hemodynamic stability during CPB. It exerts certain effect of myocardial protection, hence it is worthy of further research and clinical application. However, several limitations still exist in this study, for example, a small sample size, lack of long-term follow-up supporting the results, and failure to analyze the dose-dependent effects of dexmedetomidine on the patients. Additional multicenter, randomized, controlled studies with a larger sample size are required to further delve into the mechanisms of dexmedetomidine for myocardial protection.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Chanjuan Yu, Department of Anesthesiology, Third Affiliated Hospital (Tumor Hospital), Xinjiang Medical University, No. 789, Suzhou East Street, Xinshi District, Urumqi City 830000, Xinjiang Uygur Autonomous Region, P. R. China. Tel: +86-0991-7968088; Fax: +86-0991-7968111; E-mail: chanjuanyu32@163.com

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